## REMARKS

Claims 1-22 are pending. Claims 3, 5, 6 and 11-22 have been cancelled as being directed to a non-elected invention. Following entry of the amendments, claims 1, 2, 4 and 7-10 will be under examination. Applicants have reviewed the rejections set forth in the Office Action mailed September 9, 2004, and respectfully traverse all grounds for the reasons that follow.

### Rejections Under 35 U.S.C. § 112

Claims 1, 2, 4 and 7-10 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for use of the term "the optimal properties" and "the desired optimal function" allegedly because there is insufficient antecedent basis. Claim 1 has been amended above to conform to formal antecedent requirements. Accordingly, this ground of rejections is moot and is respectfully requested to be withdrawn.

Claims 1, 2, 4 and 7-10 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for use of the term "biochemical reaction network" allegedly because it is unclear where the biochemical reaction network is to be found or what network is to be used for the calculations recited in claim 1.

Applicant submits that the meaning of the term "biochemical reaction network" is sufficiently clear and distinct to satisfy the requirements of 35 U.S.C. § 112, second paragraph. The application describes at, for example, paragraph [0042] that a "biochemical reaction network" is:

> [A]n interrelated series of biochemical reactions that are part of a biochemical pathway or linked biochemical pathways. Many biochemical reaction networks have been identified such as metabolic reaction networks, catabolic reaction networks, polypeptide and nucleic acid synthesis reaction networks, amino acid synthesis networks, energy metabolism and so forth. Other types of biochemical reaction networks include regulatory networks including cell signaling networks, cell cycle networks, genetic networks involved in regulation of gene expression,

> such as operon regulatory networks, and actin polymerization networks that generate portions of the cytoskeleton. Most of the major cell functions rely on a network of interactive biochemical reactions.

Therefore, the application is clear as to the meaning of the objected term. A biochemical reaction network of the claimed invention includes an interrelated series of biochemical reactions that are part of a biochemical pathway or linked biochemical pathways.

The application also is clear as to where to find or what biochemical reaction network is to be used for the calculations recited in claim 1. For example, the application describes at paragraphs [0039] and [0040], respectively, that the methods of the invention can be used to design a biochemical reaction network in a computer or that they can be used for determining optimal functions of a comprehensive biochemical reaction network in a living cell. In the former specific embodiment, a reaction network is obtained by *a prior* design in a computer. In the latter specific embodiment, the network is obtained by representing a listing of biochemical reactions of a network of a living cell, for example. It is that initial listing, or a subsequent alteration of that network that can be used in the methods of the invention. (See, for example, paragraphs [0039] and [0040]). Further, the application provides descriptions at, for example, paragraphs [0033] - [0038] which exemplify one aspect of how the recited biochemical reaction networks are obtained and what network is used in the claimed invention. Finally, described throughout the application are various other origins and constructions of biochemical reaction networks that are applicable in the claimed methods of the invention. Accordingly, the use of the term "biochemical reaction network" is clear and Applicant respectfully requests that this ground of rejection be withdrawn.

Claims 1, 2, 4 and 7-10 also stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for recitation of the term "using" in connection with optimization methods to calculate optimal properties of a biochemical reaction network. These claims also stand rejected as indefinite for recitation of the term "optimization method" allegedly because it is unclear what

elements are intended by this term. The Office suggests inclusion of a positive term such as "calculating" and specifying the elements intended to accomplish this step.

Applicant submits that the terms are clear as written. Moreover, the application describes that optimization methods are computational methods used for determining optimal properties of a biochemical reaction network. In this regard, the application describes, for example, at paragraph [0050] that optimization methods are known in the art and cites therein a publication by Edwards and Palsson, *J. Biol. Chem.* 274:17410-416 (1999). Further, the application exemplifies several optimization methods that can be employed in the methods of the invention. Such optimization methods include, for example, flux balance analysis (FBA), phase plane analysis (PhPP) and a determination of a Line of Optimality (LO). As described at paragraph [0050] and elsewhere throughout the application, these and other optimization methods are computational methods that can be employed to determine optimal properties of a biochemical reaction network. Paragraph [0047] describes, for example, that optimal properties of a biochemical reaction network can be determined from a list of reactions representing a biochemical reaction network and paragraphs [0052] through [0065] exemplify the computational processes of these exemplary optimization methods.

Although clear as written, Applicant has amended claim 1 to recite that optimal properties of a biochemical reaction network are calculated by applying computational optimization methods to a list of reactions representing the biochemical reaction network. The claimed step is sufficiently clear as written, as well as in light of the descriptions in the specification, to satisfy the requirements of the second paragraph of § 112. Applicant therefore respectfully requests that this ground of rejection be withdrawn.

Claims 1, 2, 4 and 7-10 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for use of the term "recomputing" in connection with optimal properties in step (b) of claim 1. In this regard, the Office alleges that the claim fails to initially compute any parameter in light of the phrasing in step (a). As described above, claim 1 has been amended to recite that

optimal properties of a biochemical reaction network are calculated by applying computational optimization methods to a list of reactions representing the biochemical reaction network. Therefore, this ground of rejection is moot in light of this amendment and Applicant respectfully requests its withdrawal.

Claims 1, 2, 4 and 7-10 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for use of the term "evolve" allegedly because this term is defined in the art as a "change over a (long) period of time." However, the Office asserts that following construction, the cells are to be cultivated with no further evolution desired, allowing expression or detection of a desired optimal function.

The plain meaning of the term "evolution," and as it is defined in the dictionary, is understood to refer to "a series of related changes in a certain direction." *Webster's Third New International Dictionary, Unabridged.* Merriam-Webster, 2002. http://unabridged.merriam-webster.com (1 June 2004), attached as Exhibit A. The term is used consistent with its plain meaning. Cells are constructed, placed in culture under a specified environment and cultivated for a sufficient period of time and under conditions to allow a series of related changes to occur in a certain direction. The claim further recites that the direction of evolution is toward the desired optimal function. The application sets forth this meaning at, for example, paragraphs [0081] - [0084]. Accordingly, the plain meaning of the term is clear and withdrawal of this ground of rejection is respectfully requested.

**Rejections Under 35 U.S.C. § 103**

Claims 1, 2, 4 and 7-10 stand rejected under 35 U.S.C. § 103 (a) as obvious over Edwards et al. (2000) in view of Varner et al. The Office asserts that Edwards et al. describes a method of determining optimal growth in *E. coli* using metabolic flux balance analysis and that growth of engineered cells may be determine *in silico* or used to design networks. Edwards et al. does not describe culturing engineered cells to allow expression on an optimal function or the introduction or alteration of genes for industrial or research purposes. Varner et al. is asserted to describe

computer-implemented models to predict actual growth or metabolism of genetically altered and cultured cells. The Office concludes that it would have been obvious to culture engineered cells as described by Varner et al. to allow development of an optimal function, such as growth, in the methods of Edwards et al. because Edwards et al. describes designing cells for industrial and research purposes.

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed device or method to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). Establishing that the prior art would have suggested the claimed device requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (*quoting C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); *see also C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device)). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125.

The combination of Edwards et al. and Varner et al. fail to provide the requisite evidentiary showing necessary to establish a *prima facie* case of obviousness. In this regard, the cited references fail to teach or suggest calculating optimal properties of a biochemical reaction network, altering reactions and re-computing the optimal properties, constructing a genetic makeup of a cell to contain biochemical reactions specifying the optimal properties and evolving the optimal properties in a genetic makeup by cultivating the genetic makeup under a specified environment. Similarly, neither Edwards et al. or Varner et al. provide any motivation to

construct a genetic makeup of a cell containing biochemical reactions specifying optimal properties and evolving the cell to the desired optimal function under a specified environment.

Edwards et al. appears to describe the assembly of strain-specific data to define an *in silico* representation of a metabolic network for a selected group of single cellular organisms. Varner et al. appears to describe mathematical models of metabolic pathways. Neither Edwards et al. or Varner et al. teach or suggest construction of a genetic makeup of a cell containing biochemical reactions specifying optimal properties of a cell. Further, neither Edwards et al. or Varner et al. teach or suggest placing the genetic makeup in a specified environment and culturing it to evolve to the desired optimal function determined in optimization steps as the invention as describes and claims.

Instead, Edwards et al. and Varner et al. focus on whether their *in silico* modeling methods can be used to predict behavior or are sufficiently reliable for the construction of other *in silico* models. For example, Edwards et al. describes that his methods are useful for construction of other *in silico* representations and further teaches away from culturing or evolving genetic makeups of cells when Edwards states:

> The analysis of the metabolic phenotype-genotype relation using the bioinformaticaly based *in silico* metabolic genotype of *E. coli* can serve as a basis for the construction of parallel *in silico* representations of other single-cell organisms. . . . Utilizing the techniques described herein, information can be gained regarding the metabolic physiology of a cell with relatively little experimental biochemical information on the cell of interest.

Edwards et al. at page 938, col. 2, para. 3 (emphasis added).

Further, Edwards et al. describes that any culturing of cells predicted by the described model is for "experimental verification" for the "further development of *in silico* strains and their use to represent their *in vivo* counterparts." *Id.* Edwards et al. similarly does not provide any motivation to construct and evolve genetic makeups of *in silico* strains. Rather, Edwards et al.

describes that "understanding the metabolic fluxes and their control is essential to the ability to 'design' metabolic networks for the production [of] commodity chemicals (i.e., antibiotics, vitamins, amino acids, etc.)." Edwards et al. at page 938, col. 1, para. 2 (emphasis added). Thus, Edwards et al. describes that the ability to design useful *in silico* models is dependent on a correct understanding of metabolic fluxes and their control. Edwards et al. therefore fails to provide any teaching, suggestion or motivation to evolve genetic makeups of optimal biochemical reaction networks as described and claimed in the present application.

Varner et al. similarly is focused on the ability of the described mathematical models to accurately predict metabolic pathways and fails to provide any teaching, suggestion or motivation to construct and cultivate a genetic makeup of a cell containing biochemical reactions specifying optimal properties and evolving the genetic makeup to the desired optimal function determined *in silico*. In particular, Varner et al. is completely silent as to any actual construction of a genetic markup of an *in silico* model. Therefore, Varner et al. is similarly silent as to any teaching, suggestion or motivation of producing a genetic markup of an optimized biochemical reaction network and evolving that genetic markup under a specified environment to the desired optimal function determined by an optimized biochemical reaction network.

Because Edwards et al. and Varner et al. are focused on the reliability and predictability of their described models, these references fail to teach or suggest or provide motivation for an evolutionary cultivating step as claimed by the invention. Further, because these references fail to teach or suggest that an actual cell constructed to represent an optimal biochemical reaction network can require an evolutionary cultivating step in order for the genetic makeup to exhibit the desired optimal function, the evidentiary showing required for the motivation to combine these publications is lacking. Both Edwards et al. and Varner et al. conclude that their described models are sufficiently reliable to form the basis of other *in silico* models. Therefore, the references also cannot suggest or provide any motivation for an evolutionary step because they teach that such a step is unnecessary since their methods are satisfactory for the described purposes.

Accordingly, Edwards et al. and Varner et al. cannot provide any teaching, suggestion or motivation to evolve a genetic makeup of a cell to the desired optimal function as claimed by the invention. Therefore, the claimed invention is unobvious over the combination of cited references and withdrawal of this ground of rejection is respectfully requested.

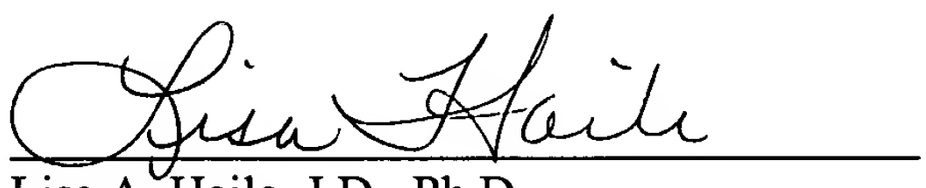
## CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Enclosed is Check No. 575577 in the amount of $510.00 for the Three (3) Months Extension of Time fee. The Commissioner is hereby authorized to charge for any additional required fees, or credit any overpayments to Depcsit Account No. 07-1896.

Respectfully submitted,

Date: March 9, 2005



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